PHENYLBUTAZONE AND ITS DERIVATIVES

WITH SPECIAL REFERENCE TO G.27202

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In 1951 Currie reported on the use of phenylbutazone in the treatment of 41 cases of "fibrositis." As a result of this work one of us (F. D. H.) became interested in this compound and began blind controlled trials with material sent to him by Currie. The following year Currie (1952) published results on his first 81 patients, Hart and Johnson (1952) on their first 16, and the new substance was generally released. Since then it has been in extensive general use, and its efficacy and also its toxic effects have become widely recognized. Many consider it to be probably the best drug available, if tolerated, in the treatment of acute gout and all stages of ankylosing spondylitis (Hart, 1958), and in some cases of rheumatoid arthritis (Mason and Hayter, 1958). We agree with the last-named authors that it is often useful in other disorders of bone, such as metastatic carcinomatosis and Paget's disease. We also use it widely in the treatment of osteoarthritis, particularly of the hips. Such a wide spectrum of therapeutic efficiency has from the beginning made us feel that the good effect of the drug lies essentially in its giving relief from pain, and we have from early days regarded it from the clinical aspect as essentially a long-acting slowly broken down analgesic, its main virtue lying in its even action over 24 hours of the day. Graham (1958) also found it useful in three out of five cases of post-herpetic neuralgia, as did Partelides (1955) in a larger series, and we have obtained pain relief in a case of disseminated sclerosis where no bone or joint disease was present.

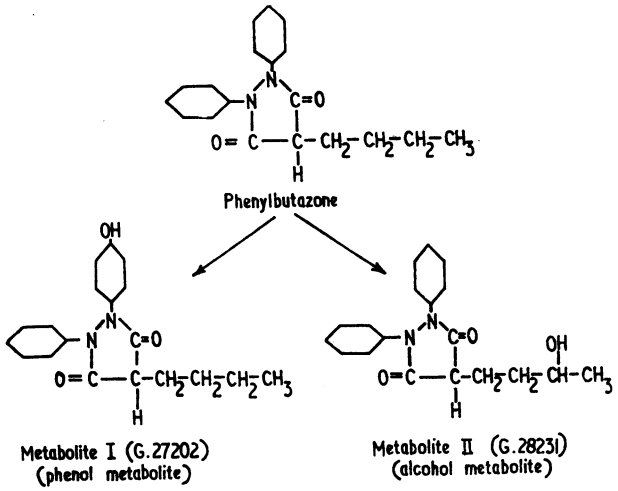
The relatively high incidence of gastro-intestinal side-effects has, however, led to increased efforts to find a derivative which would be better tolerated without significant reduction in therapeutic activity. The present paper concerns such a substance, now known as G. 27202 or "metabolite I."

Chemistry and Pharmacology

Burns *et al.* (1955b) investigated the metabolism of phenylbutazone and isolated two metabolites from the urine of patients receiving the drug. These two metabolites, metabolite I with a phenolic group in the para-position of a benzene ring, and metabolite II with an alcohol group in the butyl side-chain, are related as shown in the next column.

These two derivatives are identical with two pyrazole compounds which have been synthesized in Basle (Pfister and Häfliger, 1957; Denss *et al.*, 1957), and metabolite I, hydroxyphenyl butazone, has been designated G.27202. Biochemical analysis shows that when phenylbutazone is metabolized 3% appears in the urine as G.27202. If this substance is injected intravenously, like phenylbutazone, it disappears only slowly from the plasma, having an average biological half-life of three days (Burns *et al.*, 1953; Burns *et al.*, 1955a; Yü *et al.*, 1958). As only 4% of a given dose is excreted in the urine during this period of time it can be deduced that G.27202 is slowly but largely metabolized.

Oral absorption of G.27202 has been compared with intravenous administration in doses of 600 mg. (Yü *et al.*, 1958). Over a period of 4 to 24 hours these writers found that plasma levels were approximately the same by either route of administration, indicating extremely satisfactory absorption from the gastro-intestinal tract. With repeated orally administrated daily doses a plateau is reached in plasma level after three days; thereafter the level is constant from day to day for a given individual. The plasma levels had a range similar to that obtained with the same dosage schedule of phenylbutazone (Burns *et al.*, 1953).



The effect of G.27202 on the urinary excretion of sodium and water was also studied, as was its influence on the urinary excretion of uric acid (Yü *et al.*, 1958). It was found that, with doses of 800 mg. daily, sodium and water was retained in the body to a significant degree and similar to an equivalent dose of phenylbutazone. In contrast with phenylbutazone, however, there was no detectable uricosuria in doses of up to 800 mg. of G.27202.

Researches with metabolite II indicate that it is unlikely to be of clinical value as it is not absorbed orally, but it is interesting to note that administered intravenously, as one might have predicted, it is a potent uricosuric agent comparable to phenylbutazone and with a much reduced salt-and-water-holding power. The same workers found that various substitutions in the para-position of a benzene ring of phenylbutazone lead to compounds possessing potent "antirheumatic" and sodium-retaining activity. On the other hand, substitutions in the butyl side-chain result in compounds which have potent uricosuric activity but only mild "antirheumatic" and sodium-retaining properties.

Preliminary animal work with G.27202 has suggested that it is rather better than phenylbutazone as an anti-inflammatory and analgesic agent, the former being stressed as a result of its ability to reduce acute formalin oedema and formalin peritonitis in the rat (Domenjoz and Wilhelmi, personal communication). Also in that animal it partially inhibits the formation of inflammatory granuloma tissue (Selye's method). Of great significance to us was the finding of definite reduction in ulcerogenic activity from toxicity studies

in both dogs and rats with G.27202 as compared with the parent substance.

The promising results obtained from experimental work in both animals and humans prompted us to carry out a clinical trial with G.27202 in both in-patients and out-patients attending the rheumatism unit at Westminster Hospital.

Material and Methods

We treated 117 patients (52 male, 65 female) having the following disorders:

	Male	Female
Rheumatoid arthritis	21	41
Ankylosing spondylitis	22	3
Osteoarthritis	7	19
Psoriatic arthropathy	1	—
Paget's disease of femur	—	1
Sciatica (lumbar disk lesion)	—	1
Reiter's syndrome	1	—

Initially we set out to determine: (*a*) Whether patients obtained more or less relief of discomfort (pain and stiffness) on G.27202 as compared with phenylbutazone in the same dosage. (*b*) Which drug caused fewer symptoms of gastric intolerance. The method used was simply to substitute G.27202 for ordinary phenylbutazone dose for dose (usually 100 mg. b.d., t.d.s., or q.d.s.), the tablets being administered with meals. In all cases patients were put on each drug for one to three weeks unless gastro-intestinal symptoms necessitated discontinuing them. At the end of the trial they were asked to comment on which drug was the more effective (G>P or P>G), if both were equally effective (G=P), or if neither was effective (G=P=O). Comments on the side-effects and observations on fluid retention were also recorded.

In some of those patients who had found G.27202 effective, but less so than phenylbutazone, the dosage of G.27202 was subsequently increased to determine how much was required to obtain an equivalent effect. There were 14 patients in this group, and most of them were suffering from ankylosing spondylitis, as it was soon apparent that they were the best and most consistent observers.

In 10 cases the dose of G.27202 was increased up to 600 mg. to see whether symptoms of gastric intolerance appeared at this higher level. In 14 others the drug was continued for periods of 3 to 12 months to assess chronic toxicity.

Results

The observations on the relative effectiveness of G.27202 and phenylbutazone in the 117 patients are recorded in Table I by sex and collectively. It will be

TABLE I.—*Patients' Subjective Impressions of the Relative Effectiveness of Phenylbutazone and G.27202*

Sex	G>P	G=P	P>G	G=P=O	Total
Males	10 (19%)	17 (32%)	18 (35%)	7 (14%)	52 (100%)
Females	8 (13%)	17 (26%)	19 (29%)	21 (32%)	65 (100%)
Total	18 (15%)	34 (29%)	37 (32%)	28 (24%)	117 (100%)

Percentages are expressed separately for males, females, and the total.

seen that over twice as many females as males (32% to 14%) were not helped by either phenylbutazone or G.27202, but, excluding these, there is good agreement between the sexes as to the relative benefit obtained from the two preparations. Of the 89 patients helped by both phenylbutazone and G.27202, 34 considered the drugs to be of equal value, but of the remaining 55 twice as many thought phenylbutazone to be the stronger as thought the reverse (37 to 18).

As some patients were assessed and treated in hospital it was thought useful to see whether there were any different trends in response. The results are shown in Table II. There is little difference except that a larger

TABLE II.—*In-patients' and Out-patients' Subjective Impressions of the Relative Effectiveness of Phenylbutazone and G.27202*

	G>P	G=P	P>G	G=P=O	Total
In-patients	8 (18%)	11 (25%)	11 (25%)	14 (32%)	44 (100%)
Out-patients	10 (14%)	23 (31%)	26 (36%)	14 (19%)	73 (100%)
Total	18 (15%)	34 (29%)	37 (32%)	28 (24%)	117 (100%)

Percentages are expressed separately for in-patients, out-patients, and the total.

proportion of hospital in-patients did not benefit from either phenylbutazone or G.27202, possibly because their symptoms were more severe.

Of the 14 patients previously referred to who considered G.27202 less effective than phenylbutazone the effective dose ratio was found to be 2 to 1 in five patients, 5 to 3 in one, and 3 to 2 in eight, all in favour of phenylbutazone.

Long-term Study.—In the 14 patients treated with G.27202 for periods of 3 to 12 months there was no evidence of intolerance in any with a daily dose of 300–400 mg.

High-dosage Study.—In the 10 patients who had had gastric symptoms with phenylbutazone but who could tolerate G.27202, the dose of the latter was increased to 600 mg. daily for periods of one to three weeks. In one case mild indigestion appeared early but the remaining nine were unaffected.

Toxic and Side Effects

The number of patients who suffered from gastric intolerance with phenylbutazone was compared with those who had reacted in this way with G.27202. They were divided into those who had had mild indigestion which did not necessitate discontinuing treatment and those who had had treatment discontinued because of severe symptoms. The results are shown in Table III.

TABLE III.—*Gastric Intolerance in 117 Patients on Phenylbutazone and G.27202*

Gastric Intolerance	G.27202	Phenylbutazone
Severe symptoms	4	20
Mild ,,	6	5
Total	10	25

It will be seen that 25 out of the 117 patients had gastric intolerance to phenylbutazone whereas only 10 were similarly affected by G.27202. Furthermore, most of the cases intolerant to phenylbutazone had severe symptoms, whereas over half of those intolerant to G.27202 had mild symptoms.

Although electrolyte studies were not made, evidence of fluid retention, as measured by weight gain and ankle oedema, was noted. On phenylbutazone two patients gained weight and developed ankle oedema, and in one other there was slight weight gain. On G.27202 three patients gained weight and developed ankle oedema, and in two others there was slight weight gain. Other side-effects noted were an urticarial rash with fever which developed on the third day of G.27202 therapy and took a week to clear. Two others complained of giddiness and headache on both

phenylbutazone and G.27202; the significance of these complaints is difficult to assess. In no case was there any evidence of depression of circulating neutrophils.

Discussion

We have used phenylbutazone widely since 1952 in doses of 300–400 mg. daily, and to date we have met no case of agranulocytosis at this conservative dosage. Humble (1953) did, however, report that of 44 of our patients treated with phenylbutazone the blood clotting-time was significantly prolonged in 6 and in 14 the prothrombin time was prolonged.

Undoubtedly we would have used phenylbutazone even more widely had it not been for the occurrence of gastric intolerance in 20–25% of cases in which the therapy was instituted. In G.27202 we have a related substance which, on our experience, has a decidedly reduced liability to cause gastro-intestinal disturbance. Doses up to 600 mg. are in most cases well tolerated. This advantage is offset to some extent because, dose for dose, G.27202 appears to be a somewhat weaker pain-relieving drug than phenylbutazone.

It is true that some patients found G.27202 more effective than phenylbutazone, but many of these were intolerant of the latter, and this was sufficient to outweigh any consideration of reduced therapeutic effectiveness. We formed the opinion from a limited study, largely in cases of ankylosing spondylitis which benefited from both drugs, that phenylbutazone was more effective than G.27202 in the proportion of 3 to 2, with some patient-to-patient variation either side of this mean.

From experimental work in doses of 800 mg. daily G.27202 was shown to have a significant sodium-and-water-retaining activity comparable to that of the same dose of phenylbutazone (Yü *et al.*, 1958). In our study, using doses of 300–400 mg. daily, fluid retention was detected clinically in a small number of cases rather more with G.27202 than with phenylbutazone.

As a result of this investigation we have created a demand for G.27202 in a proportion of patients who obtain great benefit from it but who cannot tolerate phenylbutazone. This in itself is a persuasive argument for the introduction of an effective more benign phenylbutazone derivative. G.27202 goes some way to meet this demand and indicates that further adaptation of the original molecule may eventually produce the ideal "pain-relieving" preparation in the treatment of rheumatic diseases. The expression "pain relieving" is used advisedly because we have not personally observed any significant anti-inflammatory effect on swollen joints with this class of compound, and the term antirheumatic is too vague for clear interpretation.

It has already been mentioned that substitutions in the benzene ring increase the salt-retaining and pain-relieving properties of the parent substance, whereas substitutions in the butyl side-chain enhance uricosuric activity. It also appears that those substitutions which cause a reduction in the *p*K value are the ones which produce the greatest uricosuric activity, and recently the phenylthioethyl derivative of metabolite II, designated G.25671, and the sulphoxy metabolite G.28315 have been investigated (Ogryzlo and Harrison, 1957; Kersley *et al.*, 1958); both these derivatives are effective on oral administration and cause little or no gastric irritation. The above-mentioned workers have found that both these substances (G.25671 and G.28315) have a short half-life in the body and little pain-relieving activity or tendency to produce salt and water retention; for this reason they were recommended in the treatment of chronic gout, in which condition they compared favourably with other uricosuric agents. It appears to us that G.27202 is likely to be of value in the treatment of acute gout, where the possibility of giving doses up to 800 mg. daily without significant gastric toxicity will be of great advantage.

Work has to date been centred more on the uricosuric compounds than on the "antirheumatic" ones. From our series of cases we feel that further modifications may produce less toxic and more useful compounds in the treatment of a large variety of the chronic rheumatic disorders.

Summary

G.27202 (hydroxy-phenylbutazone), a metabolite of phenylbutazone, given in equal doses, has been shown to cause considerably less gastric irritation in our hands than phenylbutazone itself. Although long-term continued studies may reveal a larger number of side-effects, these have to date been infrequent and mild with a daily dose of 100–600 mg. taken orally with meals.

The pain-relieving properties of G.27202 vary from patient to patient, but overall it appears to be weaker than phenylbutazone, possibly in the ratio of 3 to 2. This reduction in effectiveness, however, only slightly offsets the more definite reduction in gastric irritation.

There are distinct advantages in using a slowly metabolized long-acting substance in the treatment of the chronic rheumatic disorders; G.27202 may well play a useful part in those cases where phenylbutazone is poorly tolerated.

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Statistics on the medical profession in Africa compiled by the W.H.O. show that in Algeria there is one doctor for every 4,958 of the population, one per 5,708 in Tunisia, 9,926 in Madagascar, 9,263 in Morocco, 9,924 in Kenya, 20,166 in the Cameroons under French trusteeship, 20,203 in Tanganyika, 20,379 in the Belgian Congo, 21,022 in Uganda, 23,028 in French Equatorial Africa, 29,197 in French West Africa, 29,761 in Liberia, 55,057 in Nigeria, 62,630 in the Cameroons under British trusteeship, and 65,146 in Ruanda-Urundi. By way of comparison with other continents, the United States has 729 inhabitants to each doctor, France 1,090, the United Kingdom 1,855, Brazil 2,993, and Indonesia 71,465 (*Science-Afrique*, No. 13, 1958).